

FACTORS INFLUENCING THE SURVIVAL OF RECIPIENTS AFTER HEART TRANSPLANTATION: A FIVE-YEAR RETROSPECTIVE STUDY

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Abstract

Introduction: Cardiac transplantation remains the standard procedure for patients with end-stage heart failure. Assessing the outcomes of heart transplantation, including mortality and its predictors, is highly important for transplant centers. The aim of this study is to explore the possible influence of the quality of life, depressive symptoms, optimism, self-efficacy, and medical data on survival among heart transplant recipients over a five-year observational period.

Material and methods: 131 heart transplant recipients were included in this study. Psychological functioning and quality of life were assessed using self-reported measures (Beck Depression Inventory, Life

Orientation Test, General Self Efficacy Scale, and World Health Organization Quality of Life). Clinical data were obtained from an electronic health record.

Results: During a median follow-up of five years, 24% of patients died. The occurrence of vascular graft disease increased the risk of death twofold in the population studied (HR = 2.17 [1.066, 14.446], $p = 0.032$). In the patients diagnosed with heart failure on the NYHA scale, the risk of death for patients with a NYHA rating of II-IV was twice as high (HR = 2.18 [1.043, 4.578], $p = 0.037$) compared with a NYHA rating of I.

Conclusions: Neither the quality of life nor psychological factors were associated with five-year survival. Only coronary artery vasculopathy and having a higher NYHA scale rating following heart transplantation were independently predictive of five-year mortality among heart transplant recipients.

Key words: heart transplantation, quality of life, survival

Introduction

Heart transplant (HTx) is a recognized surgical method for treating end-stage heart failure [1,2]. Although randomized clinical studies on heart transplants have never been conducted, there is a standard agreement that heart transplantation by surgeons with proper qualifications significantly prolongs life and improves exercise capacity and quality of life, and therefore tends to be recommended over conventional therapy [1]. According to the available results in the large databases of the International Society for Heart and Lung Transplantation (ISHLT), the median survival for cardiac recipients is 12.4 years (for HTx 2002–2008), and the median survival is 6.6 years for retransplant patients [3]. According to the Organization-Coordination Centre for Transplantation Poltransplant, the survival rate of heart transplant recipients in the Polish population is 71% in the first year, 61% over 5 years, and 47% over 10 years [4]. The survival of heart transplant recipients is affected by many modifiable and non-modifiable factors. Survival in the first year is limited by infections, heart failure, and multi-organ failure. The following years are dominated by tumors, vascular graft disease, and heart failure [3]. As many as 70% of patients remain in the New York Heart Association (NYHA) functional class I, while 20% stay in functional class II 10 years after heart transplantation [5].

Heart transplantation allows most patients with previous terminal heart failure to return to their everyday lives. Five years after transplantation, 75% of patients are not limited in their daily activities and live with no or only minimal symptoms, as indicated by a Karnofsky Index of $> 90\%$. Five years after transplantation, 38% of working-age patients work at least part-time [3,5]. Following heart transplantation, patients report improved functional capacity and overall quality of life; however, this varies depending on the severity of illness before transplantation [5]. Demographic, clinical, psychosocial, and behavioral factors are also significant predictors of long-term survival after heart transplantation. Poor quality of life and psychological well-being have increased

morbidity and mortality after transplantation [6]. A substantial portion of HTx patients' experiences depression (estimated prevalence of 20–30%) [7,8]. The elevated rates of depressive symptoms in transplant recipients may arise from stressors associated with the recovery and rehabilitation process, the need to follow a complex medical regimen, and adjustment to the prospect of new health threats, including acute and chronic graft rejection, infections, and malignancies. Additionally, pre-existing depression is more likely to persist into the post-transplant period [9]. Findings from research indicate that symptoms of depression can predict mortality in HTx patients independently of somatic and lifestyle risk factors [10]. In the literature, depressive symptoms appear to be a risk factor and prognostic marker of coronary vascular diseases (CVDs) and all-cause mortality among populations of initially healthy individuals and those with known CVD [11]. Several studies have reported no association between psychosocial factors and mortality, while others have found several psychiatric risk factors and social/demographic characteristics correlated with post-transplant morbidity [12:141;13,14]. Positive psychological constructs (e.g., optimism, self-efficacy) appear to be associated with various health outcomes (such as health-related quality of life) and recovery. In their study, Hoodin et al. found that optimism of hematopoietic stem cell transplantation patients appeared to affect their survival in the short term [15].

The main aim of this study is to explore the possible influence of the quality of life, depressive symptoms, optimism self-efficacy, and medical data on the survival among heart transplant recipients in a 5-year observational period.

Understanding the impact of biopsychosocial factors on long-term outcomes after heart transplantation can provide direction for developing appropriate therapeutic strategies.

Materials and Methods

This study was performed as a single-center cross-sectional study.

A non-random sample of participants (131 heart transplant recipients) was included in this study. The participants met the following inclusion criteria: (1) having an HTx transplant, (2) being over the age of 18 years, (3) at least three months since HTx before the commencement of the study, (4) agreeing to participate in the study, and (5) not being diagnosed with any mental health disorders.

Ethics

The study protocol was approved by the Jagiellonian University Bioethics Committee (Dnr: Nr KBET/246/B/2012). All participants gave their written informed consent, and the analysis was performed following the Declaration of Helsinki.

Methods

At the baseline, the recipients completed the following questionnaires:

a) Psychological Factors

1. The Beck Depression Inventory-Short Form. This is a 13-item short-form questionnaire with scores of 5–7 indicating mild depression, 8–15 moderate depression, and 16 or higher severe depression. The BDI-SF is used to screen for depressive symptoms. This tool has good internal consistency, with Cronbach's alpha ranging from 0.73 to 0.92 with a mean of 0.86 [16].
2. The Life Orientation Test-Revised (LOT-R). This is a 10-item measure of optimism vs. pessimism. Of the 10 items, three measure optimism, three measure pessimism, and four serve as fillers. Respondents rate each item on a 4-point scale: 0 = strongly disagree, 1 = disagree, 2 = neutral, 3 = agree, and 4 = strongly agree. Interpretation of score range: 0–13, low optimism; 14–18, moderate optimism; 19–24, high optimism [17]. The instrument has good internal consistency, with a Cronbach's alpha of 0.76 [18,19].
3. The General Self-Efficacy Scale (GSES). This assesses perceived self-efficacy regarding coping and adaptation abilities in daily activities and isolated stressful events. This self-report measure consists of 10 items, each rated on a 4-point scale. The total score ranges between 10 and 40, with a higher score indicating greater self-efficacy. Interpretation of score range: 10–24, low self-efficacy; 30–40, high self-efficacy [19]. The instrument has a good internal consistency, with Cronbach's alpha ranging from 0.78 to 0.85 [20].
4. World Health Organization Quality of Life BREF. The WHOQOL-BREF instrument comprises 26 items that measure the following broad domains: physical health, psychological health, social relationships, and environment. Each item's answers are given on a 1–5 Likert-type scale, where 1 denotes the least and 5 the highest agreement with a particular claim. A higher sum of points represents a higher quality of life in a single domain [19]. The instrument has good internal consistency, with Cronbach's alpha ranging from 0.66 to 0.84 [21].

b) Medical Factors

The following baseline medical parameters were retrieved from patients' medical records: Ejection Fraction (EF) [22], presence of Cardiac Artery Vasculopathy (CAV) [23], acute rejection episodes, malignancies, and chronic renal insufficiency [24].

The likelihood of survival was estimated for the entire group of patients who underwent a heart transplant (N = 131) from the date of the transplantation to Jul 31, 2018, while the quality of life and its determinants were estimated for a period of 5 years since the study was conducted – that is, from Jan 1, 2012, to Jul 31, 2018.

Statistical Analysis

The analysis was performed using STATISTICA software version 10.0 (StatSoft, Inc., 2011, USA).

The baseline patient characteristics were compared between the following categories:

- depressive symptoms (> 5 pts), without depressive symptoms (< 5 pts);
- high optimism (19–24 pts) vs. low optimism (0–13 pts);
- high self-efficacy (30–40 pts) vs. moderate (25–29 pts) vs. low self-efficacy (10–24 pts);
- the QOL domain was divided into moderate and high categories regarding psychological health, social relationships, and the physical domain; in the environmental domain, the comparison was between low and moderate;
- presence of morbidities (yes/no).

The endpoint was survival for a minimum period of 5 years since baseline.

The steps in the analysis were as follows:

- The significance of differences in survival between the two groups was assessed using a log-rank test (except for the EF analysis, where Cox's *f* test results were added).
- The significance of differences between a more significant number of subgroups was analyzed using a chi-square test.
- Cox proportional hazards regression was used to estimate the influence of factors on mortality in the study population. The model was constructed using the backward stepwise variable selection method to obtain a model containing only significant hazard predictors ($p < 0.05$).

In all analyses, 0.05 was adopted as the level of significance.

Results

Analysis of Sociodemographic and Clinical Factors

One hundred and thirty-one heart transplant recipients were included in this study. Men constituted 75.7% ($N = 91$) of the study group. The mean (SD) age of the patients was 54 years. The length of survival since transplantation was 10 years.

The recipients reported their overall quality of life to be excellent (62%, $N = 81$). The highest QOL score was observed in the social relationship domain (15.07, $SD = 2.39$), followed by the environment (14.20, $SD = 2.39$), psychological health (13.07, $SD = 1.11$), and physical domain QOL (13.08, $SD = 1.59$) scores. The study population's average BDI score was 6.24, with an SD of 5.31. Overall, 66 patients (50.4%) reported mild to severe symptoms of depression. The distribution of optimism (LOTR-R) results among the participants showed a mean score of 15.01, with an SD of 4.18. The total score for the GSES was

30.30, and the SD was 4.73. In the study group, most patients presented preserved left ventricular ejection fraction (mean LVEF 57.9%) and mild heart failure symptoms (93.1% of individuals in NYHA I or II scores). CAV was diagnosed in 26.7% of the recipients; 32.8% had chronic kidney disease with a mean estimated glomerular filtration rate of 59 mL/min. Baseline characteristics in groups are presented in the Table 1. Of the 131 patients, we had baseline data, 31 died within the 5-year observation period. After 5 years from the baseline, the survival rate was 76% (Figure 1).

Table 1. Baseline characteristics

Variables	Group I, N (%)	Group II, N (%)
	Better functioning	Malfunctioning
Depression	Without depressive symptoms	With depressive symptoms
	65 (49.61)	66 (50.38)
Overall subjective QOL	High scores	Low scores
	81 (62)	42 (32)
Missing data	8(6)	
Overall subjective health	87 (66.4)	44 (33.6)
Physical domain	22 (16.8)	100 (76.3)
Missing data	9(7)	
Psychological domain	15 (11.5)	108 (82.4)
Missing data	8(6)	
Social relationship	83 (63.36)	40 (30.53)
Missing data	8(6)	
Environment	58 (44.3)	65 (49.6)
Missing data	8(6)	
Optimism*	48 (36.6)	31 (23.7)
Self-efficacy	83 (63.4)	48 (36.6)
Medical variables	Without comorbidities	With comorbidities
Severe renal dysfunction	88 (67.2)	43 (32.8)
Coronary artery vasculopathy	96 (73.3)	35 (26.7)
Malignancy	112 (85.5)	19 (14.5)
Acute rejection episode	108 (82.4)	23 (17.6)
Ejection fraction	Normal left ventricular ejection fraction (> 50%)	Reduced left ventricular ejection fraction (< 40%)
	101 (77.1)	30 (22.9)
NYHA scale	I	II-IV
	102 (78.46)	28 (21.54)
Missing data	1(1)	

*recipients with high vs. low levels of optimism included

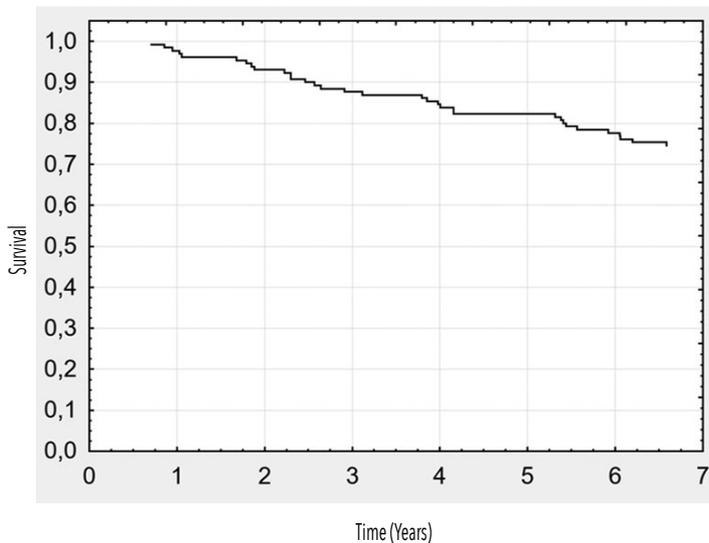


Figure 1. Kaplan-Meier curves for survival in the follow-up

Analysis of Psychological Variables and Survival Rates

The presence of depressive symptoms was not associated with the 5-year follow-up survival ($p = 0.53$). We did not find any significant difference in patient survival between the low vs. high optimism and self-efficacy groups (Table 2).

Quality of Life and Survival Rates

The specification of overall quality of life as low vs. good was not associated with 5-year survival (logrank test 0.076; $p = 0.9392$). All domains for quality of life as well as satisfaction with the patient's health condition were not found to be associated with 5-year survival ($p > 0.05$) (Table 2).

Analysis of Clinical Variables and Survival Rates

The analysis of the occurrence of diseases and survival among the study group showed that only the presence of coronary artery diseases ($p < 0.001$), a low ejection fraction (EF $< 40\%$) ($p < 0.001$), and the NYHA scale (II–IV) ($p < 0.001$) differentiated survival in the study group (Table 2 and Figure 2).

Table 2. Comparison Kaplan-Meier *survival* curves between prognostic factors

Prognostic factor	Total Number of Cases N	p-Value
<i>Depressive symptoms</i>		
Without depressive symptoms	65	> 0.05
With depressive symptoms	66	
<i>Satisfaction with health</i>		
Low scores	44	> 0.05
High scores	87	
<i>Quality of life physical domain</i>		
High scores	100	> 0.05
Low scores	22	
Missing data	9	
<i>Quality of life psychological domain</i>		
High scores	108	> 0.05
Low scores	15	
Missing data	8	
<i>Quality of life social domain</i>		
High scores	83	> 0.05
Low scores	40	
Missing data	8	
<i>Quality of life environmental domain</i>		
High scores	58	> 0.05
Low scores	65	
Missing data	8	
<i>Optimism*</i>		
Low scores	31	> 0.05
High scores	48	
<i>Self-efficacy</i>		
Low scores	48	> 0.05
High scores	83	
<i>Severe renal dysfunction</i>		
Yes	88	> 0.05
No	43	
<i>Cardiac allograft vasculopathy</i>		
Yes	35	< 0.001
No	96	
<i>Malignancy</i>		
Yes	19	> 0.05
No	112	
<i>Episode of acute rejection</i>		
Yes	23	> 0.05
No	108	
<i>Ejection fraction</i>		
Normal left ventricular ejection fraction (> 50%)	101	0.04
Reduced left ventricular ejection fraction (< 40%)	30	

Prognostic factor	Total Number of Cases N	p-Value
<i>NYHA scale</i>		
I	102	< 0.001
II–IV	28	
Missing data	1	

*recipients with high vs. low levels of optimism included

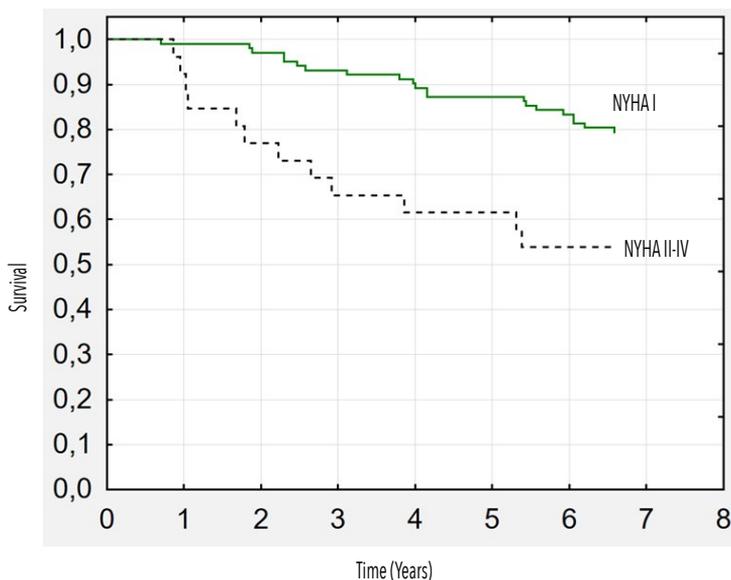


Figure 2. NYHA scale and 5-year survival; $p = 0.0036$

Model Related to Death Risk Factors in the Study Group

The simultaneous influence of numerous variables on time to death was estimated using the Cox multivariate proportional hazards model. The model was estimated using backward stepwise variable selection to obtain a model that contained only the significant hazard predictors ($p < 0.05$) (Table 3).

The occurrence of vascular graft disease significantly increased (by over two times) the risk of death in the study group ($p < 0.05$; Table 2). In post-transplant patients diagnosed with heart failure causing limited physical activity with NYHA II–IV, the risk of death was over two times higher ($p < 0.05$; Table 4, Figure 3).

Table 3. Initial model (Cox regression model)

	Effect Level	Variable	SE	χ^2	P	HR	-95% PU HR	+95% PU HR
Cardiac allograft vasculopathy	1	0.73	0.26	7.83	0.0051	4.317	1.550	12.02
Acute rejection episode	1	0.45	0.25	3.18	0.0745	2.464	0.915	6.64
Environmental domain	High	0.36	0.29	1.53	0.2157	2.058	0.657	6.45
Quality of life	1-3	0.33	0.34	0.97	0.3258	1.947	0.516	7.35
Depression	5 and more	0.32	0.30	1.14	0.2864	1.878	0.589	5.98
NYHA scale	II-IV	0.31	0.36	0.76	0.3844	1.875	0.455	7.72
Optimism	High	0.28	0.41	0.47	0.4938	1.781	0.243	13.06
Self-efficacy	High	0.27	0.44	0.37	0.5433	1.081	0.383	3.06
Social relationship domain	High	0.23	0.28	0.66	0.4156	1.584	0.523	4.80
Satisfaction with health	4-5	0.23	0.33	0.49	0.4848	1.578	0.439	5.67
Physical health domain	Moderate	0.22	0.26	0.72	0.3946	1.568	0.557	4.41
Ejection fraction	High	0.21	0.44	0.23	0.6311	1.530	0.269	8.69
Psychological domain	Moderate	0.19	0.34	0.31	0.5760	1.465	0.384	5.59
Malignancy	1	0.19	0.23	0.69	0.4073	1.457	0.598	3.55
Severe renal dysfunction	1	0.08	0.38	0.05	0.8319	1.176	0.262	5.27
Optimism	Low	0.01	0.35	0.00	0.9696	1.362	0.213	8.68
Number of morbidities	More than 1	0.01	0.33	0.00	0.9878	1.010	0.274	3.73
Self-efficacy	Low	-0.46	0.89	0.27	0.6036	0.520	0.031	8.70

HR (hazard ratio) > 1 increased risk of death

Table 4. Final model ($\chi^2 = 11.61$, $p = < 0.001$)

	Effect Level	χ^2	p	HR	-95% PU HR	+95% PU HR
Coronary artery disease	Yes	4.557	0.0328	2.177	1.066	4.446
NYHA	II-IV	4.294	0.0383	2.185	1.043	4.578

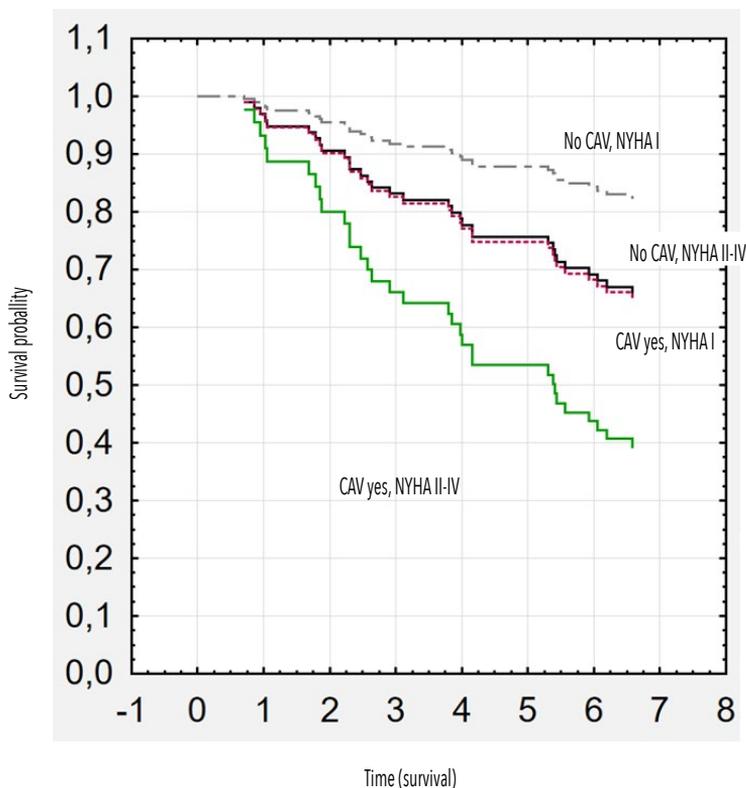


Figure 3. The comparison of survival curves depending on the occurrence of graft vascular disease and heart failure

Discussion

One of the main goals of this study was to examine the association between psychological functioning – including depressive symptoms, self-efficacy, optimism, quality of life, and medical data – and 5-year mortality following heart transplantation in a convenience sample of heart transplant recipients. Our results predicted that the presence of cardiovascular allograft vasculopathy, a low EF, and a higher score on the NYHA scale limited survival in the study group.

The most recent data of the ISHLT registry indicate a current 1-year survival rate of 84.5% and a 5-year survival rate of 72.5% [3]. Conditions such as CAV, malignancy, infection, acute rejection, and renal insufficiency significantly impact patient outcomes following heart transplantation. Five years after heart transplantation, one-third of patients are diagnosed with CAV. After ten years, CAV occurs in more than 50% of patients and substantially impacts survival [3,23,25,26]. Our results confirm that CAV limits survival. The presence of CAV

and low NYHA significantly increased (over two times higher) the risk of death in the study group. Other studies confirmed that CAV is highly prevalent in HTx recipients, and immunological and non-immunological factors can explain this. Compared to patients without CAV, the hazard ratio for death or re-transplantation was 1.22. Higher ISHLT CAV grades are independently associated with worse graft survival [19]. The data from the ISHLT registry show that comparisons within the CAV group and CAV within three years of transplant and survival in patients without CAV were significant at $p < 0.05$ [3].

Our study analyzed the impact of the quality of life, personal resources (self-efficacy and optimism), and depressive symptoms on survival prediction. None of the examined factors significantly affected the likelihood of survival in the study group. Similar results were obtained by Sponga et al., a single study in which the authors analyzed the impact of psychosocial characteristics on long-term outcomes after heart transplantation [27]. However, Havik et al. found that symptoms of depression predict mortality independently of somatic and lifestyle risk factors in HTx patients [11]. Dew et al. conducted a systematic review with a meta-analysis to examine whether depression and anxiety increase morbidity and mortality risks after transplantation. They confirmed that depression increases the risk of post-transplant mortality [9].

In their study, Previato et al. confirmed that outcomes after HTx remain constrained by the development of acute rejection and cardiac allograft vasculopathy [28]. Farmer et al. found that educational level and higher levels of social and economic satisfaction were predictive of improved survival among heart transplant recipients 5 years after transplantation. Conversely, marital status, more cumulative infections, the presence of hematologic disorders, a higher NYHA class, and poor adherence to medical care predicted worse survival [14]. In a study that examined the relationship between negative effects early after lung transplantation and long-term survival, the authors found that higher levels of depression and general distress, but not anxiety, as measured six months following lung transplantation, were associated with increased mortality, independent of background characteristics and medical predictors [29].

Conclusions

In our study, neither quality of life nor psychological factors were associated with 5-year survival. However, we confirmed that coronary artery vasculopathy and a higher NYHA scale following heart transplantation independently predict 5-year mortality (survival) among heart transplant recipients. Hence, a higher NYHA class should prompt investigations of severe cardiovascular disorders.

The early detection of coronary artery vasculopathy and revascularization strategies for patients who develop CAV is key to therapy management. The

transplant team should determine the optimal regimen for administering immunosuppressive and conventional risk factor-modifying agents.

Also, the transplant team should help patients live a poor-quality long life, especially those with the presence of medical complications.

Study Limitations

Our study has several limitations. First, it was a single-center analysis, meaning the results should be interpreted with caution. Unfortunately, data on psychological welfare – especially depression assessment before transplant – which is highly relevant to the study of all-cause mortality, were unavailable.

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Czynniki wpływające na przeżycie biorców po transplantacji serca: 5-letnie badanie retrospekcyjne

Streszczenie

Wprowadzenie: Przeszczepienie serca pozostaje standardem postępowania w leczeniu schyłkowej niewydolności serca. Ocena wyników przeszczepu serca, w tym śmiertelności i jej czynników prognostycznych, jest bardzo ważna dla ośrodków transplantacyjnych. Celem pracy jest zbadanie możliwego wpływu jakości życia, objawów depresyjnych, optymizmu, poczucia własnej skuteczności oraz danych medycznych na przeżycie wśród biorców serca w 5-letnim okresie obserwacji.

Material i metody: Badaniem objęto 131 biorców przeszczepu serca. Funkcjonowanie psychologiczne i jakość życia oceniano za pomocą samoopisowych skal (Inwentarz Depresji Becka, Test Orientacji Życiowej, Skala Uogólnionej Własnej Skuteczności oraz Jakość Życia Światowej Organizacji Zdrowia). Dane kliniczne uzyskano z elektronicznego rekordu pacjenta.

Wyniki: W okresie obserwacji o medianie 5 lat zmarło 24% pacjentów. Wystąpienie choroby naczyniowej graftu dwukrotnie zwiększało ryzyko zgonu w badanej populacji ($HR = 2,17 [1,066, 14,446]$, $p = 0,032$). U pacjentów z rozpoznaną niewydolnością serca w skali NYHA II-IV ryzyko zgonu pacjentów było dwukrotnie wyższe ($HR = 2,18 [1,043, 4,578]$, $p = 0,037$) w porównaniu z oceną NYHA I.

Wnioski: Ani jakość życia, ani czynniki psychologiczne nie były związane z 5-letnim przeżyciem. Jedynie waskulopatia tętnic wieńcowych i wyższa skala NYHA po przeszczepieniu serca były niezależnymi predyktorami 5-letniej śmiertelności wśród biorców serca.

Słowa kluczowe: przeszczep serca, jakość życia, przeżycie